FORM PTO-1390 (REV. 9-2001) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
MUR-032-USA-PCT	
U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	
10/031747	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/04945	July 25, 2000	July 27, 1999

TITLE OF INVENTION

Patch Formulation For External Use

APPLICANT(S) FOR DO/EO/US Hideharu Chono, Tōshiro Yamaguchi, Hisakazu Kurita, Tetsuro Tateishi and Naruhito Higo

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [X] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [X] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [X] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [X] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [X] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [X] Other items or information: Claim For Priority

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) 10/031747	INTERNATIONAL APPLICATION NO. PCT/JP00/04945	ATTORNEY'S DOCKET NUMBER MUR-032-USA-PCT

21. [X] The following fees are submitted:

	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ -0-	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$	
Total claims	26 - 20 =	-6-	x **$18.00**	$ 108.00	
Independent claims	2 - 3 =	-0-	x **$84.00**	$ -0-	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$280.00**	$ -0-	
TOTAL OF ABOVE CALCULATIONS =				$ 998.00	
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +				$ -0-	
SUBTOTAL =				$ 998.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$ -0-	
TOTAL NATIONAL FEE =				$ 998.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 40.00	
TOTAL FEES ENCLOSED =				$ 1038.00	
				Amount to be refunded:	$
				charged:	$

a. [X] A check in the amount of $ 1038.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. ____________ in the amount of $ ________ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 20-1424 A duplicate copy of this sheet is enclosed.

d. [ ] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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[signature]
SIGNATURE

Donald E. Townsend
NAME

22,069
REGISTRATION NUMBER

MUR-032-USA-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of
H. CHONO, et al.

International Application No.: **PCT/JP00/04945**

International Filing Date: **25 July 2000**

Title: **Patch Formulation For External Use**

PRELIMINARY AMENDMENT

BOX PCT
Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

After assigning a serial number to the above-captioned application and before calculating the fee, please undertake the following changes:

IN THE CLAIMS

Please substitute the amended claims 1-20 for the original claims:

1. (Amended) A patch formulation for external use, comprising a basic drug, an organic acid and an organic acid salt as essential components.

2. (Amended) The patch formulation for external use according to claim 1, wherein the basic drug is an acid addition salt thereof.

3. (Amended) The patch formulation for external use according to claim 1, wherein the organic acid is a carboxylic acid having carbon atoms of 2 to 7.

4. (Amended) The patch formulation for external use according to claim 1, wherein the organic acid is at least one acid selected from the group consisting of acetic, lactic, tartaric, citric, malic, benzoic and salicylic acids.

5. (Amended) The patch formulation for external use according to claim 1, wherein the organic acid salt is a metal salt of a carboxylic acid.

6. (Amended) The patch formulation for external use according to claim 1, wherein the organic acid salt is sodium acetate.

7. (Amended) The patch formulation for external use according to claim 1, comprising 0.1 to 20% by weight of the basic drug, 0.01 to 20% by weight of the organic acid and 0.01 to 20% by weight of the organic acid salt, based on the total weight of the composition of the adhesive layer.

8. (Amended) The patch formulation for external use according to claim 2, wherein the ratio of the acid addition salt of the basic drug to the organic acid salt, ranges from 5:1 to 1:5 (by equivalent ratio).

9. (Amended) The patch formulation for external use according to claim 2, wherein the ratio of the acid addition salt of the basic drug tot he organic acid, ranges from 5:1 to 1:5 (by equivalent ratio).

10. (Amended) The patch formulation for external use according to claim 1, wherein the ratio of the organic acid to the organic acid salt, ranges from 3:1 to 1:20 (by equivalent ratio).

11. (Amended) The patch formulation for external use according to claim 2, wherein the acid addition salt of the basic drug is at least one agent selected from the group consisting of hypnotics/sedatives, antipyretic anti-inflammatory analgesics, antimigraine agents, stimulants/antihypnotics, anti-psychoneurotics, local anesthetics, agents for urinary organs, skeletal muscle relaxants, agents for autonomous nerves, anti-Parkinsonian agents, antihistamines, bronchodilators, cardiotonics, coronary vasodilators, peripheral vasodilators, agents for circulatory organs, antiarrhythmics, antiallergics, antidizzying agents, anti-serotonin-receptor antiemetics and narcotic analgesics.

12. (Amended) A patch formulation for external use, wherein said patch formulation is obtained with a basic drug, an organic acid and an organic acid salt as essential components.

13. (Amended) The patch formulation for external use according to claim 12, wherein the basic drug is an acid addition salt thereof.

14. (Amended) The patch formulation for external use according to claim 12, wherein the organic acid is a carboxylic acid having carbon atoms of 2 to 7.

15. (Amended) The patch formulation for external use according to claim 12, wherein the organic acid salt is a metal salt of a carboxylic acid.

16. (Amended) The patch formulation for external use according to claim 12, wherein the patch formulation is obtained by using 0.1 to 20% by weight of the basic drug, 0.01 to 20% by weight of the organic acid and 0.01 to 20% by weight of the organic acid salt, based on the total weight of the composition of the adhesive layer.

17. (Amended) The patch formulation for external use according to claim 13, wherein said patch formulation is obtained with the ratio of the acid addition salt of the basic drug to the organic acid salt, ranging from 5:1 to 1:5 (by equivalent ratio).

18. (Amended) The patch formulation for external use according to claim 13, wherein said patch formulation is obtained with the ratio of the acid addition salt of the basic drug to the organic acid, ranging from 5:1 to 1:5 (by equivalent ratio).

19. (Amended) The patch formulation for external use according to claim 12, wherein said patch formulation is obtained with the ratio of the organic acid to the organic acid salt, ranging from 3:1 to 1:20 (by equivalent ratio).

20. (Amended) The patch formulation for external use according to claim 13, wherein the acid addition salt of the basic drug is at least one agent selected from the group consisting of hypnotics/sedatives, antipyretic anti-inflammatory analgesics, antimigraine agents, stimulants/antihypnotics, anti-psychoneurotics, local anesthetics, agents for urinary organs, skeletal muscle relaxants, agents for autonomous nerves, anti-Parkinsonian agents, antihistamines, bronchodilators, cardiotonics, coronary vasodilators, peripheral vasodilators, agents for circulatory organs, antiarrhythmics, antiallergics, antidizzying agents, anti-serotonin-receptor antiemetics and narcotic analgesics.

Please add new claims 21-26 as follows:

21. The patch formulation for external use according to claim 2, characterized in that the organic acid is at least one acid selected from the group consisting of acetic, lactic, tartaric, citric, malic, benzoic and salicylic acids.

22. The patch formulation for external use according to claim 3, characterized in that the organic acid is at least one acid selected from the group consisting of acetic, lactic, tartaric, citric, malic, benzoic and salicylic acids.

23. The patch formulation for external use according to claim 2, characterized in that the organic acid salt is sodium acetate.

24. The patch formulation for external use according to claim 3, characterized in that the organic acid salt is sodium acetate.

25. The patch formulation for external use according to claim 4, characterized in that the organic acid salt is sodium acetate.

26. The patch formulation for external use according to claim 5, characterized in that the organic acid salt is sodium acetate.

REMARKS

The amendments to Claims 1-20, and the addition of new claims 21-26, are made to eliminate the multiple dependencies and to place the claims in proper U.S. format. The effect of the foregoing amendments relate only to matters of form, and the substance of the claims remain the same. The present amendment is deemed not to add new matter. Claims 1-26 are in the application.

It is respectfully submitted that this application is now in condition for examination on the merits and early action and allowance thereof is accordingly respectfully requested.

Respectfully submitted,

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Date: January 24, 2002

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MARKED-UP VERSIONS OF AMENDED CLAIMS 1-20:

1. (Amended) A patch formulation for external use, [characterized by] comprising a basic drug, an organic acid and an organic acid salt as essential components.

2. (Amended) The patch formulation for external use according to claim 1, [characterized in that] wherein the basic drug is an acid addition salt thereof.

3. (Amended) The patch formulation for external use according to claim 1, [characterized in that] wherein the organic acid is a carboxylic acid having carbon atoms of 2 to 7.

4. (Amended) The patch formulation for external use according to claim 1 [or 3], [characterized in that] wherein the organic acid is at least one acid selected from the group consisting of acetic, lactic, tartaric, citric, malic, benzoic and salicylic acids.

5. (Amended) The patch formulation for external use according to claim 1, [characterized in that] wherein the organic acid salt is a metal salt of a carboxylic acid.

6. (Amended) The patch formulation for external use according to claim 1 [or 5], [characterized in that] wherein the organic acid salt is sodium acetate.

7. (Amended) The patch formulation for external use according to claim 1, [characterized by] comprising 0.1 to 20% by weight of the basic drug, 0.01 to 20% by weight of the organic acid and 0.01 to 20% by weight of the organic acid salt, based on the total weight of the composition of the adhesive layer.

8. (Amended) The patch formulation for external use according to claim 2, [characterized in that] wherein the ratio of the acid addition salt of the basic drug to the organic acid salt, ranges from 5:1 to 1:5 (by equivalent ratio).

9. (Amended) The patch formulation for external use according to claim 2, [characterized in that] wherein the ratio of the acid addition salt of the basic drug tot he organic acid, ranges from 5:1 to 1:5 (by equivalent ratio).

10. (Amended) The patch formulation for external use according to claim 1, [characterized in that] wherein the ratio of the organic acid to the organic acid salt, ranges from 3:1 to 1:20 (by equivalent ratio).

11. (Amended) The patch formulation for external use according to claim 2, [characterized in that] wherein the acid addition salt of the basic drug is at least one agent selected from the group consisting of hypnotics/sedatives, antipyretic anti-inflammatory analgesics, antimigraine agents, stimulants/antihypnotics, anti-psychoneurotics, local anesthetics, agents for urinary organs, skeletal muscle relaxants, agents for autonomous nerves, anti-Parkinsonian agents, antihistamines, bronchodilators, cardiotonics, coronary vasodilators, peripheral vasodilators, agents for circulatory organs, antiarrhythmics, antiallergics, antidizzying agents, anti-serotonin-receptor antiemetics and narcotic analgesics.

12. (Amended) A patch formulation for external use, [characterized in that] wherein said patch formulation is obtained with a basic drug, an organic acid and an organic acid salt as essential components.

13. (Amended) The patch formulation for external use according to claim 12, [characterized in that] wherein the basic drug is an acid addition salt thereof.

14. (Amended) The patch formulation for external use according to claim 12, [characterized in that] wherein the organic acid is a carboxylic acid having carbon atoms of 2 to 7.

15. (Amended) The patch formulation for external use according to claim 12, [characterized in that] wherein the organic acid salt is a metal salt of a carboxylic acid.

16. (Amended) The patch formulation for external use according to claim 12, [characterized in that] wherein the patch formulation is obtained by using 0.1 to 20% by weight of the basic drug, 0.01 to 20% by weight of the organic acid and 0.01 to 20% by weight of the organic acid salt, based on the total weight of the composition of the adhesive layer.

17. (Amended) The patch formulation for external use according to claim 13, [characterized in that] wherein said patch formulation is obtained with the ratio of the acid addition salt of the basic drug to the organic acid salt, ranging from 5:1 to 1:5 (by equivalent ratio).

18. (Amended) The patch formulation for external use according to claim 13, [characterized in that] wherein said patch formulation is obtained with the ratio of the acid addition salt of the basic drug to the organic acid, ranging from 5:1 to 1:5 (by equivalent ratio).

19. (Amended) The patch formulation for external use according to claim 12, [characterized in that] wherein said patch formulation is obtained with the ratio of the organic acid to the organic acid salt, ranging from 3:1 to 1:20 (by equivalent ratio).

20. (Amended) The patch formulation for external use according to claim 13, [characterized in that] wherein the acid addition salt of the basic drug is at least one agent selected from the group consisting of hypnotics/sedatives, antipyretic anti-inflammatory analgesics, antimigraine agents, stimulants/antihypnotics, anti-psychoneurotics, local anesthetics, agents for urinary organs, skeletal muscle relaxants, agents for autonomous nerves, anti-Parkinsonian agents, antihistamines, bronchodilators, cardiotonics, coronary vasodilators, peripheral vasodilators, agents for circulatory organs, antiarrhythmics, antiallergics, antidizzying agents, anti-serotonin-receptor antiemetics and narcotic analgesics.

SPECIFICATION

PATCH FORMULATION FOR EXTERNAL USE

Technical Field

The present invention relates to a patch formulation for external use. In particular, the invention relates to a patch formulation for external use comprising a basic drug, an organic acid and an organic acid salt, having a good percutaneous absorption property and good stability.

Background Art

Conventionally, various methods for administrating drug have been known such as oral, rectal, intracutaneous or intravenous administration, and among them oral administration is employed most widely. However, oral administration has some defaults, for example, that a drug is prone to a first pass effect in the liver, and that the blood level of a drug becomes transiently higher than that required after it is administered orally. In addition, such adverse reactions as gastrointestinal disturbance, nausea, anorexia and so on have been often reported after oral administration. Furthermore, considering an increase in the number of patients with difficulty in deglutition in this aged society, pharmaceutical formulations easier to take are required clinically. Therefore, patch formulations for external use have been actively developed and such products are also marketed, because they can eliminate these defaults

of oral administration and can be taken more safely and more continually by patients as pharmaceutical formulation easy to take.

But, many drugs have so low percutaneous absorption that their patch formulations for external use are difficult to develop, thus hindering such formulations from functioning adequately. In other words, normal skin has inherently a barrier function to prevent foreign bodies from intruding into the body, whereby many drugs are not well absorbed percutaneously when a typical base is used for such patch formulations.

It has thus been attempted to elevate percutaneous absorption of drugs through the corneal layer of epidermis, generally by means of addition of a so-called percutaneous absorption enhancer into the base. For example, absorption promoting compositions comprising a lower alkyl amide, such as a combination of dimethyl acetamide with ethyl alcohol, isopropyl alcohol or isopropyl palmitate (U. S. Patent No. 3,472,931); a combination of 2-pyrrolidone with a suitable oil, or a straight-chain fatty acid with an alcoholic ester (U. S. Patent No. 4,017,641); a lower alcohol and an alcohol having carbon atoms of 7 to 20, an aliphatic acid hydrocarbon having carbon atoms of 5 to 30, an alcoholic ester of an aliphatic carboxylic acid having carbon atoms of 19 to 26, a mono- or di-ether having carbon atoms of 10 to 24 or a combination of a ketone having carbon atoms of 11 to 15 (Japanese Patent Laid-Open No. 61-249934) and the like were disclosed. However, these conventional absorption

enhancers and absorption promoting compositions are not sufficiently safe to the skin. In addition, in a patch formulation for external use containing a basic drug in the form of an acid addition salt, the drug could hardly be expected to exhibit its effect.

Further, a technique of using a combination of a drug and an organic acid is also described for patch formulations for external use. For example, a tape formulation where betamethasone valerate and an organic acid are combined together with a natural rubber based adhesive (Japanese Patent Laid-Open No. 56-61312), a tape formulation where a non-steroidal anti-inflammatory analgesic and an organic acid are combined together with an acrylic adhesive (Japanese Patent Laid-Open No. 62-126119), also a poultice-type formulation where methyl salicylate as a drug component, an emulsifier, an organic acid, a plasticizer, a tackifying resin and water are combined together with styrene-isoprene-styrene block copolymer (Japanese Patent Laid-Open No. 63-159315) and the like were disclosed. In any of these specifications, however, no organic acid salt is used, and the organic acid is used to improve stability, elevate solubility and adjust pH, but not to elevate percutaneous absorption of the drug. Furthermore, any drug in these specifications is acidic or neutral, and use of the organic acid therein is not intended to elevate either skin permeation or stability of a basic drug through ion pair formation as in the present invention.

Also, another technique is attempted to elevate skin

permeation of a basic physiologically active substance. For example, a tape formulation where citric acid and isoproterenol hydrochloride are combined together with an acrylic adhesive (Japanese Patent Laid-Open No. 63-79820), and a tape formulation where an organic acid and vinpocetine are combined together with an acrylic adhesive (Japanese Patent Laid-Open No. 5-25039) were described. However, these formulations have a problem of irritability when detached, and they cannot release a sufficient amount of a drug for therapy.

Also, yet another technique of combining a drug and an organic acid as a percutaneous dosage formulation is disclosed. For example, a formulation containing an organic acid and a glycol together with a salt of a non-steroidal anti-inflammatory analgesic (Japanese Patent Laid-Open No. 62-181226), and a patch formulation comprising an alkaline metal salt of a non-steroidal anti-inflammatory analgesic and an organic acid more acidic than the free form of the non-steroidal anti-inflammatory analgesic (Japanese Patent Publication No. 7-47535) were described. These disclosures, however, do not relate to basic drugs but to acidic drugs. Also disclosed is a formulation where a basic drug or its salt, an alcohol having carbon atoms of 2 to 5, an organic acid having carbon atoms of 2 to 5 and a carboxylic acid ester having carbon atoms of 16 to 20 are combined, although application of an organic acid salt is not described therein.

Yet another technique to formulate a patch formulation is disclosed in WO 96/16642, where an organic acid salt is

contained together with the salt form of a basic drug, but it is not disclosed that a combination of an organic acid with an organic acid salt may elevate the skin permeability of the drug, nor the physical stability of the patch formulation for external use, such as adhesiveness or appearance.

Accordingly, no patch formulation for external use has yet been known that contains a basic drug in the form of an acid addition salt, thereby possessing excellent stability and also a desirable percutaneous absorption property of the drug therein.

Disclosure of the Invention

The objects of the present invention is to dissolve the above mentioned problems of the prior art and to provide a patch formulation for external use comprising a basic drug, which has a good percutaneous absorption property of the drug and good stability.

After many efforts to dissolve the above mentioned problems, the inventors have found that, by including particular amounts of an organic acid and an organic acid salt into a patch formulation for external use which contains a basic drug in the form of an acid addition salt, more stable ion pairs are formed therein than in a patch including the organic acid salt alone, and a quasi-stable state, capable of elevating skin permeability of the drug therein, can be maintained constantly therein, and the finding has resulted in completion of the present invention.

Accordingly, the present invention relates to a patch

formulation for external use characterized by that it contains a basic drug, an organic acid and an organic acid salt as essential components.

Best Mode for Carrying Out the Invention

The invention will be described in detail below.

A patch formulation for external use according to the present invention preferably comprises a adhesive layer, and further may comprise, for example, a backing layer for supporting the adhesive layer and a release liner established on the adhesive layer. Preferably, the patch formulation according to the present invention comprises a basic drug, an organic acid and an organic acid salt in the adhesive layer.

In the patch formulation according to the present invention, the basic drug used in the adhesive layer is preferably as an acid addition salt of the basic drug. The acid addition salts of the basic drug are not limited in particular, but include, for example, hypnotics/sedatives (for example, flurazepam hydrochloride, rilmazafone hydrochloride), antipyretic anti-inflammatory analgesics (for example, butorphanol tartrate, perisoxal citrate), antimigraine agents (for example, ergotamine tartrate, ergotamine mesilate), stimulants/antihypnotics (for example, methamphetamine hydrochloride, methyl phenidate hydrochloride), anti-psychoneurotics (for example, chlorpromazine hydrochloride, imipramine hydrochloride), local anesthetics (for example, lidocaine hydrochloride, procaine hydrochloride), agents for urinary organs (for

example, oxybutynin hydrochloride), skeletal muscle relaxants (for example, tizanidine hydrochloride, eperizone hydrochloride, pridinol mesilate), agents for autonomous nerves (for example, carpronium chloride, neostigmine bromide), anti-Parkinsonian agents (for example, pergolide mesilate, bromocriptine mesilate, trihexyphenidyl hydrochloride, amantadine hydrochloride), antihistamines (for example, clemastine fumarate, diphenhydramine tannate), bronchodilators (for example, tulobuterol hydrochloride, procaterol hydrochloride), cardiotonics (for example, isoprenaline hydrochloride, dopamine hydrochloride), coronary vasodilators (for example, diltiazem hydrochloride, verapamil hydrochloride), peripheral vasodilators (for example, nicametate citrate, tolazoline hydrochloride), agents for circulatory organs (for example, flunarizine hydrochloride, nicardipine hydrochloride, benidipine hydrochloride, efonidipine hydrochloride, bisoprolol fumarate, timolol maleate, diltiazem hydrochloride, metoprolol tartrate), antiarrhythmics (for example, propranolol hydrochloride, alprenolol hydrochloride), antiallergics (for example, ketotifen fumarate, azelastine hydrochloride), antidizzying agents (for example, betahistine mesilate, diphenidol hydrochloride), anti-serotonin-receptor antiemetics (for example, ondansetron hydrochloride, granisetron hydrochloride) and narcotic analgesics (for example, morphine hydrochloride, fentanyl citrate).

These basic drugs may be used alone or in combination,

and in either form of inorganic or organic salts. The basic drug may be added preferably in the range from 0.1 to 20% by weight of the total weight of the composition of the adhesive layer, considering sufficient skin permeation as a patch formulation and the effect on the adhesive property. Addition of less than 0.1% by weight of the drug results in an insufficient potency, while addition of more than 20% by weight results in a poor physical property as a patch formulation.

In the patch formulation for external use according to the present invention, the organic acid used in the adhesive layer is not limited in particular, but preferably a carboxylic acid having carbon atoms of 2 to 7. Such organic acids having carbon atoms of 2 to 7 include aliphatic mono-, di- or tri-carboxylic acids (for example, acetic, propionic, isobutyric, lactic, maleic, fumaric, pyruvic, oxalic, succinic and tartaric acids), and aromatic carboxylic acids (for example, salicylic and benzoic acids). In particular, acetic, lactic, tartaric, citric, malic, benzoic and salicylic acids are preferable among these.

These organic acids may be used alone or in combination. These organic acids may be added preferably in the range from 0.01 to 20% by weight of the total weight of the composition of the adhesive layer, more preferably from 0.1 to 15% by weight, most preferably from 0.1 to 10% by weight, considering stability and skin irritation of the patch formulation. Addition of less than 0.01% by weight of the organic acid into the adhesive layer results in poor stability, while addition

of more than 20% by weight results in skin irritation.

The ratio of the acid addition salt of the basic drug to the organic acid, when they are compounded, preferably ranges from 5:1 to 1:5 (by equivalent ratio). If the ratio of the acid addition salt of the basic drug to the organic acid is out of the range from 5:1 to 1:5, both stability and skin permeability will be reduced.

In the patch formulation for external use according to the present invention, the organic acid salt used in the adhesive layer is not limited in particular, but respective water soluble inorganic salts of aliphatic mono-, di- or tri-carboxylic acids (for example, acetic, propionic, isobutyric, caproic, caprylic, lactic, maleic, pyruvic, oxalic, succinic and tartaric acids), aromatic carboxylic acids (for example, phthalic, salicylic, benzoic and acetyl salicylic acids), alkyl sulfonic acids (for example, ethane sulfonic acid, propyl sulfonic acid, butane sulfonic acid and polyoxyethylene alkyl ether sulfonic acid), alkyl sulfonic acid derivatives (for example, N-2-hydroxyetylpiperidine-N' -2-ethane sulfonic acid (abbreviated as HEPES below)) and cholic acid derivatives (for example, dehydrocholic acid), may be exemplified. Among these, metal carboxylates are preferable, and sodium acetate is especially preferable. Although these organic acid salts may be dehydrated or hydrated, they are preferably a dehydrate when they are used in a hydrophobic adhesive layer.

These organic acid salts may be used alone or in combination. These organic acid salts may be added

preferably in a range from 0.01 to 20% by weight of the total weight of the composition of the adhesive layer, more preferably from 0.1 to 15% by weight, most preferably from 0.1 to 10% by weight, considering skin permeability and skin irritation of the patch formulation. Addition of less than 0.01% by weight of the organic acid salt results in poor skin permeability, while addition of more than 20% by weight results in skin irritation.

The ratio of the acid addition salt of the basic drug to the organic acid salt, preferably ranges from 5:1 to 1:5 (by equivalent ratio). If the ratio of the acid addition salt of the basic drug to the organic acid salt is out of the range from 5:1 to 1:5, both skin permeability and physical property will deteriorate.

Furthermore, the ratio of the organic acid to the organic acid salt, preferably ranges from 3:1 to 1:20 (by equivalent ratio), more preferably from 2:1 to 1:15 (by equivalent ratio), and most preferably from 1:1 to 1:10 (by equivalent ratio). If the ratio of the organic acid to the organic acid salt is out of the range from 3:1 to 1:20, both skin permeability and stability will be decreased.

In the patch formulation for external use according to the present invention, the adhesive layer may contain not only the basic drug, the organic acid and the organic acid salt as essential components described above, but also an absorption enhanncer, a plasticizer, a lipophilic/ hydrophobic polymer, a tackifying resin and other additives, if required.

Any compound that is known to promote the absorption of a drug by the skin may be suitable as absorption enhancer, such as a fatty acid, an aliphatic alcohol, a fatty acid ester or ether, each having carbon atoms of 6 to 20; an aromatic organic acid, an aromatic alcohol, an aromatic organic acid ester or ether (the above compounds may be saturated or unsaturated, and cyclic, linear or branched.); in addition, a lactate ester, an acetate ester, a monoterpene-type compound, a sesquiterpene-type compound, Azone, an Azone derivative, a glycerol fatty acid ester, a sorbitan fatty acid ester (Span type), a polysorbate (Tween type), a polyethylene glycol fatty acid ester, a polyoxyethylene-hardened castor oil (HCO type) or a sucrose fatty acid ester.

Preferable examples of the above described absorption enhancer are caprylic acid, capric acid, caproic acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, lauryl alcohol, myristyl alcohol, oleyl alcohol, cetyl alcohol, methyl laurate, isopropyl myristate, myristyl myristate, octyldodecyl myristate, cetyl palmitate, salicylic acid, methyl salicylate, ethylene glycol salicylate, cinnamic acid, methyl cinnamate, cresol, cetyl lactate, ethyl acetate, propyl acetate, geraniol, thymol, eugenol, terpineol, 1-menthol, borneol, d-limonene, isoeugenol, isoborneol, nerol, dl-camphor, glycerol mono-laurate, glycerol mono-oleate, sorbitan mono-laurate, sucrose mono-laurate, polysorbate 20, propylene glycol, polyethylene glycol mono-laurate, polyethylene glycol mono-stearate, HCO-60, pyrothiodecane

and others, and especially preferable examples are lauryl alcohol, l-menthol, propylene glycol and pyrrothiodecane.

These absorption enhancers may be used alone or in combination. These absorption enhancers may be added preferably in the range from 0.01 to 20% by weight of the total weight of the composition of the adhesive layer, more preferably from 0.05 to 10% by weight, most preferably from 0.1 to 5% by weight, considering skin permeability and skin irritation, such as erythema or edema, of the patch formulation.

In the patch formulation for external use according to the present invention, the plasticizer used in the adhesive layer is a petroleum-based oil (for example, paraffinic process oil, naphthenic process oil or aromatic process oil), squalane, squalene, a vegetable oil (for example, olive oil, camellia oil, castor oil, tolu oil or peanut oil), silicone oil, a dibasic acid ester (for example, dibutyl phthalate or dioctyl phthalate), a liquid rubber (for example, polybutene or liquid isoprene rubber), diethylene glycol, polyethylene glycol, glycol salicylate, propylene glycol, dipropylene glycol, triacetin, triethyl citrate, crotamiton or diethyl sebacate. Among these, liquid paraffin, liquid polybutene, glycol salicylate and crotamiton are especially preferable.

These plasticizers may be used alone or in combination. These plasticizers may be added in total preferably in the range from 10 to 70% by weight of the total weight of the composition of the adhesive layer, more preferably from 10 to 60% by weight, most preferably from 10 to 50% by weight,

so as to have good skin permeability and maintain good cohesion as a patch formulation.

In the patch formulation for external use according to the present invention, the lipophilic/hydrophobic polymer used in the adhesive layer is styrene-isoprene-styrene block copolymer (abbreviated as "SIS" below), isoprene rubber, polyisobutylene (abbreviated as "PIB" below), styrene-butadiene-styrene block copolymer (abbreviated as "SBS" below), styrene-butadien rubber (abbreviated as "SBR" below) or an acrylic polymer (a copolymer of at least two monomers selected from the group consisting of 2-ethylhexyl acrylate, vinyl acetate, methacrylates, methoxyethyl acrylate and acrylic acid). Among these, SIS, PIB, blends of SIS and PIB, and acrylic polymers are especially preferable.

These hydrophobic polymers may be used alone or in combination. A hydrophobic polymer such as SIS, PIB or the like may be added preferably in the range from 10 to 60% by weight by weight of the total weight of the composition of the adhesive layer, more preferably from 15 to 50% by weight, and most preferably from 18 to 40% by weight, so as to form the adhesive layer and have good skin permeability as a patch formulation. An acrylic polymer may be added preferably in the range from 10 to 98% by weight, more preferably from 20 to 98% by weight, and most preferably from 30 to 98% by weight on the same basis.

In the patch formulation for external use according to the present invention, the tackifying resin used in the adhesive layer is a rosin derivative (for example, rosin,

rosin glycerol ester, hydrogenated rosin, hydrogenated rosin glycerol ester or pentaerythritol rosin ester), alicyclic saturated hydrocarbon resin, aliphatic hydrocarbon resin, terpene resin or maleate resin. Among these, hydrogenated rosin glycerol ester, alicyclic saturated hydrocarbon resin, aliphatic hydrocarbon resin and terpene resin are especially preferable.

These tackifying resins may be used alone or in combination. These tackifying resins may be added preferably in the range from 10 to 70% by weight of the total weight of the composition of the adhesive layer, more preferably from 15 to 60% by weight, and most preferably from 20 to 50% by weight, considering adhesive strength and skin irritation upon detachment of the patch formulation.

In the patch formulation for external use according to the present invention, the adhesive layer may contain additives such as antioxidant, filler, crosslinker, preservative and UV absorber, if required.

Examples of antioxidants include tocopherols and ester derivatives thereof, ascorbic acid, stearoyl ascorbate, nordihydroguaiaretic acid, dibutyl-hydroxytoluene (BHT) and butyl-hydroxyanisole.

Examples of fillers include calcium carbonate, magnesium carbonate, silicates (for example, aluminum silicate and magnesium silicate), silicic acid, barium sulfate, calcium sulfate, calcium zincate, zinc oxide and titanium dioxide.

Examples of crosslinkers include thermoset resin, such

as amino resin, phenol resin, epoxy resin, alkyd resin and unsaturated polyester, isocyanate compounds, blocked isocyanate compounds, organic crosslinkers and inorganic crosslinkers, such as metals or metallic compounds.

Examples of preservatives include ethyl p-hydroxybenzoate, propyl p-hydroxybenzoate and butyl p-hydroxybenzoate.

Examples of UV absorbers include p-aminobenzoic acid derivatives, anthranilic acid derivatives, salicylic acid derivatives, coumarin derivatives, compounds based on amino acids, imidazoline derivatives, pyrimidine derivatives and dioxane derivatives.

In the patch formulation for external use according to the present invention, these additives, such as antioxidant, filler, crosslinker, preservative and UV absorber, may be added preferably at 10% by weight or less in total of the total weight of the composition of the adhesive layer, more preferably at 5% by weight or less, and most preferably at 2% by weight or less.

A process of producing a patch formulation according to the present invention, having a composition described above and for external use, may not be limited but any applicable one. As an example, after thermally melting a matrix composition containing a drug and then coating it on a piece of release paper or a substrate, the coating can be attached to the substrate or a piece of the release paper in order to prepare the patch formulation. In addition, after dissolving the matrix composition containing the drug in a

solvent, such as toluene, hexane or ethyl acetate, then casting the solution on a piece of the release paper or the substrate, and further drying the coating by solvent evaporation, the coating can be attached to the substrate or a piece of the release paper in order to prepare the patch formulation.

The patch formulation for external use according to the present invention is preferably a non-water soluble system, containing no water.

Further, provided that the patch formulation for external use according to the present invention comprises a basic drug, an organic acid salt and an organic acid, the other composition or the material of any other component may be of any type or any kind.

The backing layer, which can be established to support the adhesive layer, can be formed from an elastic or non-elastic substrate. The substrate can be selected from, for example, cloth, unwoven cloth, polyurethane, polyester, polyvinyl acetate, polyvinylidene chloride, polyethylene, polyethylene terephthalate, aluminum sheet and composite materials thereof.

The release liner, which can be established on the adhesive layer, can be formed by using film made of, for example, polyethylene terephthalate, polyester, polyvinyl chloride or polyvinylidene chloride, or laminated film of quality paper or the like with polyolefin, each film being siliconized on the side contacting the adhesive layer.

Examples

The present invention will be described in more detail by means of the following examples. In the Examples, Comparative Examples and Test Examples, "%" is always intended to mean "% by weight".

(Example 1)

Sodium acetate	1.0%
Tartaric acid	0.5%
Acrylic adhesive polymer (PE-300: Nippon Carbide Industries)	93.5%
Isocyanate crosslinker (CK-100: Nippon Carbide Industries)	1.0%
Pyrothiodecane	2.0%
Tizanidine hydrochloride	2.0%
Total	100.0%

From among these components, tartaric acid, sodium acetate, pyrothiodecane and tizanidine hydrochloride were added to ethyl acetate and then stirred at room temperature to dissolve them. Then, a solution of the acrylic adhesive polymer in ethyl acetate and the isocyanate crosslinker were added and stirred, and the solution thus obtained was cast on a film of polyethylene terephthalate (PET: 30 μm). The coating was crosslinked thermally at 90°C for 15 minuets to form an adhesive layer 50 μm thick, and thereafter a patch formulation according to the present invention was prepared.

(Example 2)

Sodium acetate	9.0%
Lactic acid	2.0%
Liquid paraffin	14.0%
Rosin adhesive	29.0%

(KE-311: Arakawa Chemical Industries)	
PIB	13.0%
SIS	18.0%
Oxybutynin hydrochloride	15.0%
Total	100.0%

From among these, the components except sodium acetate, lactic acid and oxybutynin hydrochloride were dissolved and mixed in toluene. Then, the remaining components were added and dispersed until the mixture became homogeneous, and it was then cast on a film of PET (30 μm) so as to form an adhesive layer 50 μm thick. Thereafter, a patch formulation according to the present invention was prepared.

(Example 3)	
Sodium acetate	9.0%
Citric acid	2.5%
Liquid paraffin	10.5%
Polyterpene tackifying resin (ARKON P-100: Arakawa Chemical Industries)	32.0%
PIB	13.0%
SIS	18.0%
Oxybutynin hydrochloride	15.0%
Total	100.0%

From among these, the components except sodium acetate, citric acid and oxybutynin hydrochloride were dissolved and mixed in toluene. Then, the remaining components were added and dispersed until the mixture became homogeneous, and it was then cast on a film of PET (30 μm) so as to form an adhesive layer 50 μm thick. Thereafter, a patch formulation according to the present invention was prepared.

(Example 4)

Sodium acetate	1.0%
Malic acid	0.3%
Liquid paraffin	27.4%
Rosin adhesive (KE-311: Arakawa Chemical Industries)	27.5%
PIB	12.0%
SIS	22.3%
Pyrothiodecane	3.0%
Crotamiton	5.0%
BHT	0.5%
Tizanidine hydrochloride	1.0%
Total	100.0%

From among these, the components except sodium acetate, malic acid and tizanidine hydrochloride were dissolved and mixed in cyclohexane. Then, the remaining components were added and dispersed until the mixture became homogeneous, and it was then cast on a film of PET (30 μm) so as to form an adhesive layer 50 μm thick. Thereafter, a patch formulation according to the present invention was prepared.

(Example 5)

Sodium acetate	1.0%
Benzoic acid	0.3%
Liquid paraffin	27.4%
Rosin adhesive (KE-311: Arakawa Chemical Industries)	27.5%
PIB	12.0%
SIS	22.3%
Pyrothiodecane	3.0%
Crotamiton	5.0%
BHT	0.5%

Tizanidine hydrochloride	1.0%
Total	100.0%

From among these, the components except sodium acetate, benzoic acid and tizanidine hydrochloride were dissolved and mixed in cyclohexane. Then, the remaining components were added and dispersed until the mixture became homogeneous, and it was then cast on a film of PET (30 μm) so as to form an adhesive layer 50 μm thick. Thereafter, a patch formulation according to the present invention was prepared.

(Example 6)

Sodium acetate	1.0%
Salicylic acid	0.3%
Liquid paraffin	27.4%
Rosin adhesive (KE-311: Arakawa Chemical Industries)	27.5%
PIB	12.0%
SIS	22.3%
Pyrothiodecane	3.0%
Crotamiton	5.0%
BHT	0.5%
Tizanidine hydrochloride	1.0%
Total	100.0%

From among these, the components except sodium acetate, salicylic acid and tizanidine hydrochloride were dissolved and mixed in cyclohexane. Then, the remaining components were added and dispersed until the mixture became homogeneous, and it was then cast on a film of PET (30 μm) so as to form an adhesive layer 50 μm thick. Thereafter, a patch formulation according to the present invention was prepared.

(Comparative Examples 1 to 6)

Comparative Examples 1 to 6 correspond to Examples 1 to 6, respectively, and these procedures followed those of Examples 1 to 6, respectively, except for no addition of sodium acetate used in Examples 1 to 6, to prepare a patch formulation according to the present invention.

(Comparative Examples 7 to 9)

Comparative Examples 7 to 9 correspond to Examples 1 to 3, respectively, and these procedures followed those of Examples 1 to 3, respectively, except for no addition of the respective organic acids used in Examples 1 to 3, to prepare a patch formulation according to the present invention.

(Comparative Example 10)

Comparative Example 10 corresponds to Example 4, and this procedure followed that of Example 4, except for no addition of the organic acid used in Example 4, to prepare a patch formulation according to the present invention.

(Test Example 1: In Vitro Testing of Percutaneous Absorption)

Portions of the dorsal skin were excised in hairless mice (aged from 6 to 9 weeks). After each portion was carefully removed of fat on the dermal side, it was set in the flow-through cell so that the dermal side could contact the receptor phase. Further, in the flow-through cell, water kept at 37°C was circulated outside of the receptor phase. Each patch (with an area of 5 cm^2 where the drug formulation was applied) that was prepared in Examples 1 to 6 and comparative Examples 1 to 10 was attached onto the corneal layer of each portion of isolated dorsal skin, and then the

receptor phase, i.e., physiological saline was flown at the rate of approximately 5 ml per hour. A small fraction of the saline was sampled every 2 hours until 24 hours passed after the start, while the flow rate of the receptor phase was precisely monitored. Thereafter, each sample from the receptor phase was analyzed with respect to drug concentration by high performance liquid chromatography in order to calculate cumulative skin permeation, Q, of the drug according to the following equation.

Accumulated skin permeation [Q] ($\mu g/cm^2$)

= [drug concentration ($\mu g/ml$) × flow (ml)] / applied area of the drug formulation (cm^2)

Flux of skin permeation is defined as a change in the permeation per unit time, and expressed using time, t, as follows:

flux ($\mu g/cm^2/hr$) = ΔQ ($\mu g/cm^2$)/Δt (hr)

The greater the value of flux for a formulation, the better percutaneous absorption therefrom. The results are shown in Table 1.

(Test Example 2: Testing of Formulation Stability)

Each patch for external use that was prepared in Examples 1 to 6 and Comparative Examples 1 to 10 was stored at 25°C for 3 months, and then directly observed to see if crystallization had occurred or not therein. In case crystallization occurs with the lapse of time, the appearance of the patch changes which is the checkpoint of its quality, and thus it is not rated stable as a pharmaceutical formulation. Furthermore, crystallization alters the

release characteristic and the adhesive property of the formulation, which reasons further that it is unstable. The results are also shown in Table 1.

. Overall Evaluation of Percutaneous Absorption and Formulation Stability

With respect to Examples 1 to 6 and Comparative Examples 1 to 10, an example where both percutaneous absorption and formulation stability were rated good was marked with an open circle, although an example where only one or neither of these properties was good was marked with a cross, based on the results of the above Test Examples 1 and 2. The results are also shown in Table 1.

Table 1

	Percutaneous absorption (flux of skin permeation) ($\mu g/cm^2/hr$)	Physical stability of formulation (crystallizability)	Overall evaluation of percutaneous absorption and formulation stability
Example 1	3.8	No crystallization	○
2	23.0	No crystallization	○
3	27.0	No crystallization	○
4	4.7	No crystallization	○
5	5.4	No crystallization	○
6	4.0	No crystallization	○
Comparative Example 1	0.2	No crystallization	×
2	1.0	No crystallization	×
3	0.9	No crystallization	×
4	0.2	No crystallization	×
5	0.2	No crystallization	×
6	0.1	No crystallization	×
7	3.2	Crystallization	×
8	19.1	Crystallization	×
9	22.1	Crystallization	×
10	3.8	Crystallization	×

As evident from the results shown in Table 1, the patches for external use of Examples 1 to 6 where a basic drug, an organic acid and an organic acid salt were combined were good in both percutaneous absorption and stability. On the contrary, the patches for external use of Comparative Examples 1 to 6 where only a basic drug and an organic acid were combined were good in stability but very low in percutaneous absorption. Further, the patches for external use from comparative Examples 7 to 10 where only a basic drug and an organic acid salt were combined were good in percutaneous absorption but very poor in stability.

Industrial Applicability

The present invention provides a patch formulation comprising a basic drug, and having a good percutaneous

absorption property of the drug therein and good stability.

CLAIMS

1. A patch formulation for external use, characterized by comprising a basic drug, an organic acid and an organic acid salt as essential components.

2. The patch formulation for external use according to claim 1, characterized in that the basic drug is an acid addition salt thereof.

3. The patch formulation for external use according to claim 1, characterized in that the organic acid is a carboxylic acid having carbon atoms of 2 to 7.

4. The patch formulation for external use according to claim 1 or 3, characterized in that the organic acid is at least one acid selected from the group consisting of acetic, lactic, tartaric, citric, malic, benzoic and salicylic acids.

5. The patch formulation for external use according to claim 1, characterized in that the organic acid salt is a metal salt of a carboxylic acid.

6. The patch formulation for external use according to claim 1 or 5, characterized in that the organic acid salt is sodium acetate.

7. The patch formulation for external use according to claim 1, characterized by comprising 0.1 to 20% by weight of the basic drug, 0.01 to 20% by weight of the organic acid and 0.01 to 20% by weight of the organic acid salt, based on the total weight of the composition of the adhesive layer.

8. The patch formulation for external use according to claim 2, characterized in that the ratio of the acid addition salt

of the basic drug to the organic acid salt, ranges from 5:1 to 1:5 (by equivalent ratio).

9. The patch formulation for external use according to claim 2, characterized in that the ratio of the acid addition salt of the basic drug to the organic acid, ranges from 5:1 to 1:5 (by equivalent ratio).

10. The patch formulation for external use according to claim 1, characterized in that the ratio of the organic acid to the organic acid salt, ranges from 3:1 to 1:20 (by equivalent ratio).

11. The patch formulation for external use according to claim 2, characterized in that the acid addition salt of the basic drug is at least one agent selected from the group consisting of hypnotics/sedatives, antipyretic anti-inflammatory analgesics, antimigraine agents, stimulants/antihypnotics, anti-psychoneurotics, local anesthetics, agents for urinary organs, skeletal muscle relaxants, agents for autonomous nerves, anti-Parkinsonian agents, antihistamines, bronchodilators, cardiotonics, coronary vasodilators, peripheral vasodilators, agents for circulatory organs, antiarrhythmics, antiallergics, antidizzying agents, anti-serotonin-receptor antiemetics and narcotic analgesics.

12. A patch formulation for external use, characterized in that said patch formulation is obtained with a basic drug, an organic acid and an organic acid salt as essential components.

13. The patch formulation for external use according to claim

12, characterized in that the basic drug is an acid addition salt thereof.

14. The patch formulation for external use according to claim 12, characterized in that the organic acid is a carboxylic acid having carbon atoms of 2 to 7.

15. The patch formulation for external use according to claim 12, characterized in that the organic acid salt is a metal salt of a carboxylic acid.

16. The patch formulation for external use according to claim 12, characterized in that the patch formulation is obtained by using 0.1 to 20% by weight of the basic drug, 0.01 to 20% by weight of the organic acid and 0.01 to 20% by weight of the organic acid salt, based on the total weight of the composition of the adhesive layer.

17. The patch formulation for external use according to claim 13, characterized in that said patch formulation is obtained with the ratio of the acid addition salt of the basic drug to the organic acid salt, ranging from 5:1 to 1:5 (by equivalent ratio).

18. The patch formulation for external use according to claim 13, characterized in that said patch formulation is obtained with the ratio of the acid addition salt of the basic drug to the organic acid, ranging from 5:1 to 1:5 (by equivalent ratio).

19. The patch formulation for external use according to claim 12, characterized in that said patch formulation is obtained with the ratio of the organic acid to the organic acid salt, ranging from 3:1 to 1:20 (by equivalent ratio).

20. The patch formulation for external use according to claim 13, characterized in that the acid addition salt of the basic drug is at least one agent selected from the group consisting of hypnotics/sedatives, antipyretic anti-inflammatory analgesics, antimigraine agents, stimulants/antihypnotics, anti-psychoneurotics, local anesthetics, agents for urinary organs, skeletal muscle relaxants, agents for autonomous nerves, anti-Parkinsonian agents, antihistamines, bronchodilators, cardiotonics, coronary vasodilators, peripheral vasodilators, agents for circulatory organs, antiarrhythmics, antiallergics, antidizzying agents, anti-serotonin-receptor antiemetics and narcotic analgesics.

ATTORNEY DOCKET NO: MUR-032-USA-PCT

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PATCH FORMULATION FOR EXTERNAL USE

the specification of which is ☒ attached and/or ☐ was filed on ..... as Application Serial No. ..... and was amended on (if applicable) .....

☒ international (PCT) application No. PCT/JP00/04945 filed July 25, 2000 and as amended on ..... (if any).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

COUNTRY	APPLICATION NUMBER	DATE OF FILING	PRIORITY CLAIMED UNDER 35 U.S.C. 119
JAPAN	11/212921	July 27, 1999	☒ YES ☐ NO
			☐ YES ☐ NO

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION NUMBER	DATE OF FILING	STATUS (Patented, Pending, Abandoned)

(2)

I hereby appoint the following attorneys to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: Law Offices of Townsend & Banta: Donald E. Townsend, Registration No. 22,069; ~~Roger S. Borek, Registration No. 34,343;~~ and Donald E. Townsend, Jr., Registration No. 43,198

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

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Listing of Inventors Continued on Page 2 hereof. ☒ Yes ☐ No

ATTORNEY DOCKET NO: MUR-032-USA-PCT

Listing of Inventors Continued from Page 1 of Declaration and Power of Attorney for invention entitled:

PATCH FORMULATION FOR EXTERNAL USE

3-00

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